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An efficient synthesis of (±)-panduratin A and (±)-isopanduratin A, inhibitors of dengue-2 viral activity

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ABSTRACT

Panduratin A and its regioisomer isopanduratin A are synthesized in four steps from (*E*)-ocimene, [(*E*)-3,7-dimethyl-1,3,6-octatriene] via a Diels–Alder cycloaddition reaction.

Panduratin A and its regioisomer isopanduratin A are cyclohexenyl chalcone natural products that show a wide spectrum of biological activity.[1] It has recently been reported that panduratin A and hydroxypanduratin A (Fig. 1), isolated from *Boesenbergia rotunda* (L.) showed good inhibitory activities towards dengue-2 virus NS3 protease with K_i values of 25 and 21 μM, respectively.[2] While a number of syntheses of cyclohexenyl chalcones have been described,[3] surprisingly the synthesis of panduratin A has never been reported. Herein, we report an efficient method for the synthesis of (±)-panduratin A and (±)-isopanduratin A through Diels–Alder cyclization of 2′-hydroxy-4′-methoxy-6′-ethoxymethoxychalcone and (*E*)-ocimene.

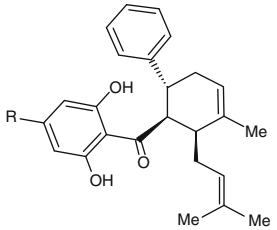
Our studies began with model reactions between 2′,4′,6′-trihydroxychalcone **1** and 2,3-dimethyl-1,3-butadiene, carried out in various solvents as well as without solvent. Heating the two compounds for an extended period of time at 110 °C resulted in the formation of 5,7-dihydroxyflavanone (Table 1). The use of Lewis acid catalysts such as $BF_3{\cdot}Et_2O$, $AlCl_3$ and $ZnCl_2$, however, resulted in extensive polymerization of the diene.

The reaction was also carried out with 2′,4′,6′-trimethoxychalcone **2** (as the dienophile) and 2,3-dimethyl-1,3-butadiene. Initial reaction (Table 1, entry 5) performed at room temperature with 1 equiv of diene in dry toluene gave no product even after 30 h of stirring. Increasing the equivalence of diene also resulted in a similar observation. When the reactants were placed in a pressure tube and heated at 50 °C for 18 h, a small amount of the expected product was obtained (Table 1, entry 6). However, increasing the temperature to 120 °C and stirring overnight in a pressure tube resulted in the Diels–Alder adduct **5** being isolated in 93% yield (Table 1, entry 7).

Following the conditions described in Table 1, entry 7, compounds **4**, **6**–**8** and their regioisomers **4a**, **6a**, **7a** and **8a** were prepared in excellent yields and no polymerization of the diene (described as a complex mixture in Table 1) was observed. The products were isolated in a 3:2 *para*/*meta* ratio and the structure of the major product (the *para* isomer) for each reaction is given in Table 2.

The Diels–Alder reaction (Table 2, entry c) was first carried out under the same reaction conditions as those of entry 7 (Table 1) where excess ocimene was used and the reaction mixture was heated at 120 °C in a pressure tube. However, no Diels–Alder adduct was isolated even after the reaction was left for 24 h. The isolated product indicated polymerization of ocimene instead. The use of various Lewis acids to catalyze the reaction also resulted in polymerization of the acid-sensitive terminal conjugated double bond in ocimene.

Ocimene can exist in the *E*- or *Z*-configuration in nature (Scheme 1). When pure (*Z*)-ocimene was reacted with chalcone **2**, no Diels–Alder adduct was isolated. Instead, polymerization of the ocimene was observed. However, when a mixture of (*E*)- and



R = OMe : panduratin A
R = OH : hydroxypanduratin A

Figure 1. Panduratin A and hydroxypanduratin A.

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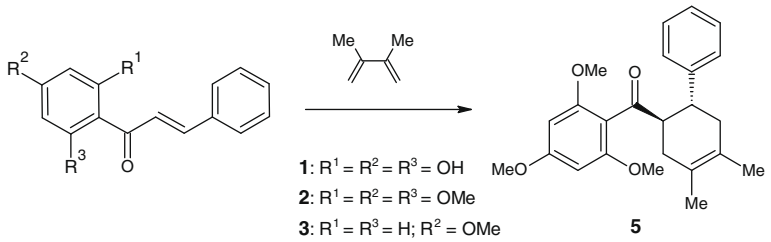
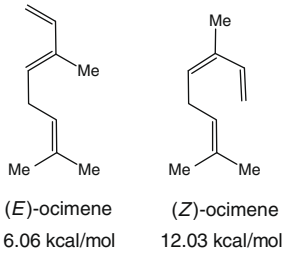
Table 1
Screening of the reaction conditions[a]



Entry	Dienophile	Temp (°C)	Time (h)	Catalyst (equiv)	Solvent	Product; yield[b] (%)
1	**1**	110	2	—	—	[c]
2	**1**–**3**	−78 (1 h)–rt	24	$ZnCl_2$ (1)	Et_2O	[d]
3	**1**, **2**	0 (1 h)–rt	24	$AlCl_3$ (1)	Toluene	[d]
4	**1**, **2**	0 (1 h)–rt	24	$BF_3{\cdot}Et_2O$ (1)	Et_2O	[d]
5	**2**	rt	30	—	Toluene	—
6	**2**	50	18	—	Toluene	**5** (30)[e]
7	**2**	120	24	—	—	**5** (93)[e]

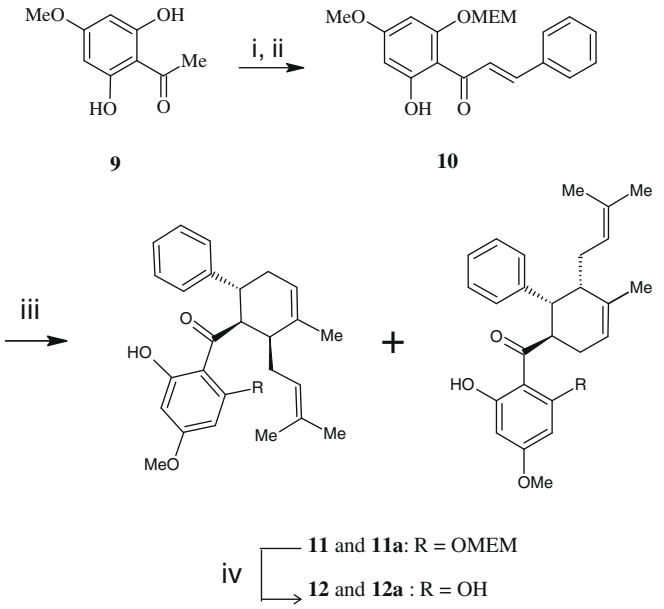
[a] Reaction conditions: dienophile (1 mmol), N_2 atmosphere.
[b] Isolated yield.
[c] Formation of 5,7-dihydroflavanone.
[d] Complex mixture obtained but no adduct was formed.
[e] Reaction performed in a pressure tube.



Scheme 1. *s-cis* Conformations of (*E*)-and (*Z*)-ocimene.

(*Z*)-ocimene was used in the Diels–Alder reaction with chalcone **2**, the adducts **6** and **6a** were isolated (Table 2).[4] Presumably, only (*E*)-ocimene underwent the Diels–Alder reaction. Examination of (*Z*)-ocimene indicated that the presence of a *Z*-prenyl substituent as part of the 1,3-butadiene moiety reduces its reactivity by hindering the approach of the dienophile. This limitation is not observed with (*E*)-ocimene. Molecular Mechanics calculations (MM+) revealed (*E*)-ocimene to be more stable than the *Z* isomer by about 6 kcal/mol. This observation could provide some rationale for our findings, where the reaction between trimethoxychalcone and a mixture of (*E*)- and (*Z*)-ocimene resulted in the formation of adducts **6** and **6a** while no product was observed when the reaction was conducted with (*Z*)-ocimene only.[5]

The synthesis of panduratin A and its regioisomer is illustrated in Scheme 2. Protection of the hydroxy group of commercially available 2′,6′-dihydroxy-4′-methoxyacetophenone **9** with 1-chloro-2-methoxyethane (MEM-Cl) followed by Claisen condensation with benzaldehyde in the presence of aqueous KOH in ethanol gave chalcone **10** in 85% yield. Reaction of chalcone **10** with 5 equiv of (*E*)-ocimene[4] at 150 °C led to the formation of a mixture of cycloadduct **11** and **11a** in quantitative

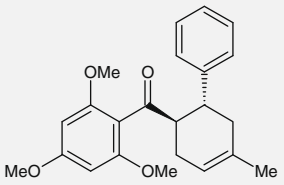
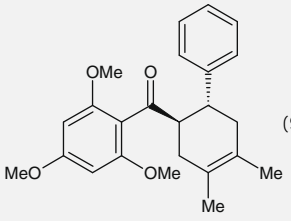
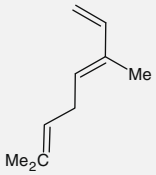
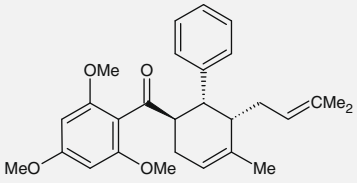
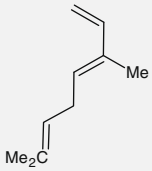
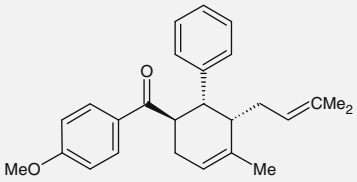
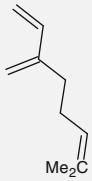
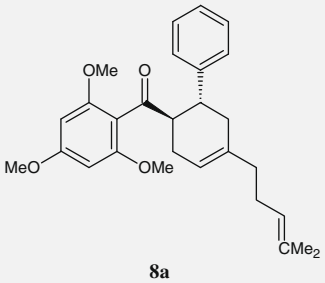


Scheme 2. Reagents and conditions: (i) MEM-Cl, dry acetone, K_2CO_3, rt, 8 h; (ii) benzaldehyde, 50% aq KOH, EtOH, 24 h, 85% over two steps; (iii) (*E*)-ocimene, 150 °C, pressure tube, 24 h; (iv) 3 M HCl, MeOH, 80 °C, 10 min, 89% over two steps.

yield. Deprotection of the MEM group gave panduratin A **12** and isopanduratin **12a** as a mixture in 89% yield.

In conclusion, we have reported a four-step synthesis of panduratin and isopanduratin A in 75% overall yield. Excellent yields are achieved for panduratin derivatives with various dienes. The syntheses involved a Diels–Alder reaction with a variety of dienes under moderate conditions (100–150 °C, neutral environment and no catalyst).

Table 2
Syntheses of panduratin A derivatives[a]

Entry	Dienophile; diene	Conditions	Product[b] (yield, %)
a	Dienophile = **2**; diene = 	120 °C, Pressure tube, 24 h	 **4a** *para*/*meta*: 3:2 (86)
b	Dienophile = **2**; Diene = 	120 °C, Pressure tube, 18 h	 (93) **5**
c	Dienophile = **2**; Diene =  (E)-Ocimene	150 °C, Pressure tube, 15 h	 **6a** *para*/*meta*: 3:2 (99)
d	Dienophile = **3**; Diene =  (E)-Ocimene	150 °C, Pressure tube, 14 h	 **7a** *para*/*meta*: 3:2 (96)
e	Dienophile = **2**; Diene =  Myrcene	120 °C, Pressure tube, 24 h	 **8a** *para*/*meta*: 3:2 (89)

[a] All products were identified by ^{1}H, ^{13}C, DEPT, COSY, HMQC, HMBC and H2BC NMR spectroscopy.
[b] Isolated yields (mixture of regioisomers), based on chalcone.

Acknowledgements

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Supplementary data

Supplementary data (general procedures and spectral data of all new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.11.030.

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4. Ocimene is sold by International Flavors and Fragrances as a mixture of *E* and *Z* isomers. For the total synthesis of (*E*)-ocimene from isoprene see Chou, T. S.; Tso, H. H.; Chang, L. J. *Chem. Commun.* **1984**, 1323–1324.
5. (*Z*)-Ocimene can be purchased from Sigma–Aldrich. (*E*)-Ocimene is thermally more stable than (*Z*)-ocimene. See Wolinsky, J.; Chollar, B.; Baird, M. D. *J. Am. Chem. Soc.* **1962**, *84*, 2775–2779.